

## REMARKS

The presently claimed invention features nucleic acid molecules related to nucleic acid molecules derived from a strain of *Xenorhabdus bovienii*. The nucleic acid molecules encode polypeptides that are toxic to certain nematodes.

### Deposit under the Budapest Treaty

*Xenorhabdus* strains H31, I73 and C42 were deposited under the terms of the Budapest Treaty and the strains will be irrevocably released without restriction or conditions upon the issuance of a patent. The deposit forms and letters confirming the deposit are attached as Exhibit A.

### Sequence Compliance

The Examiner noted that the figures include nucleotide and amino acid sequences, yet a sequence listing was not submitted previously. A sequence listing in compliance with 37 C.F.R. §1.821 – §1.825 is submitted herewith.

### Abstract

The application did not contain an abstract. An abstract is added by the present amendment. No new matter is added.

### Rejections Under 35 U.S.C. §112, first paragraph (written description)

The Examiner rejected previously pending claims 12-16 and 29 as allegedly failing to meet the written description requirement of 35 U.S.C. §112, first paragraph.

The Examiner, citing *Regents of the University of California v. Eli Lilly & Co.* 119 F.3d 1559 (Fed. Cir. 1997), stated that the claims do not meet the written description requirement because, according to the Examiner, the *Xenorhabdus* polypeptides of SEQ ID NO:22 and 23 are “not representative of the claimed genus.”

Certain of newly added claims 31-52 are drawn to nucleic acid molecules that are defined by their sequence or by the sequence of a polypeptide which they encode. Other of newly added claims are defined by the sequence of a polypeptide which they encode, which polypeptide is defined by its percent identity to a reference sequence and by its toxicity to a nematode. Thus, all of the claimed nucleic acid molecules are defined either by sequence or by sequence and function. In addition, the specification provides a several working examples of any assay for testing whether a given nucleic acid molecule encodes a polypeptide that is toxic to a nematode (see pages 31-37 of the specification).

As the Court of Appeals for Federal Circuit explained in *Eli Lilly*, an adequate written description of genetic material “requires a precise definition, such as by structure, formula, chemical name, or physical properties” *Eli Lilly* 119 F.3d at 1563. The presently claimed nucleic acid molecules are defined by sequence or by sequence combined with function. Thus, the present claims meet the written description requirement as articulated by the court in *Eli Lilly*. Moreover, The Synopsis of Written Description Guidelines published by the United States Patent and Trademark Office (the “Guidelines”) includes an example of a claim drawn to a protein defined by sequence and function (ability to catalyze a particular reaction) and supported by a specification disclosing an assay for the specified function. The Guidelines state that such claims can meet the written description requirement.

In view of the forgoing, Applicants respectfully submit that the rejection based on the written description requirement of 35 U.S.C. §112, first paragraph be withdrawn.

Rejections Under 35 U.S.C. §112, first paragraph (enablement)

The Examiner rejected previously pending claims 12-16 and 29 as allegedly failing to meet the enablement requirement of 35 U.S.C. §112, first paragraph.

The Examiner argued that the claims are not enabled because it would require undue experimentation “to predict the structures of variants to the claimed sequences that would be biologically active”. In making this argument the Examiner cited an article by Rudinger

published in 1976 that stated that identifying active variants of a peptide hormone requires "case to case painstaking experimental study".

The present claims are drawn to nucleic acid molecules that include a nucleotide sequence encoding a particular polypeptide or a polypeptide having a particular percent identity (70%, 75%, 80%, 85%, 90%, 95%, or 98%) to a reference polypeptide (SEQ ID NO:22 or SEQ ID NO:23). The specification teaches straight forward assay for determining whether a nucleic acid molecule encodes a polypeptide that is toxic to a nematode (see pages 31-37 of the specification). Briefly, the assay entails introducing the nucleic acid into an expression vector to create an expression construct that is used to transform *E. coli* that are grown in multi-well culture dishes to generate a library of clones. *C. elegans* larvae are added to the *E. coli* cultures and the cultures are visually examined several days later to assess nematode development. Thus, the assay is well suited to high throughput library screening. Indeed, high throughput library screening was used to initially identify cHRIM5 as a clone encoding a polypeptide(s) toxic to a nematode (see page 31 of the specification).

Given the teachings of the specification, one skilled in the art could make and use the nucleic acids without undue experimentation because the specification teaches one skilled in the art how to identify nucleic acid molecules encoding biologically active polypeptides. The Court of Appeals for the Federal Circuit has identified eight factors that must be considered in determining whether undue experimentation would be required to practice a claimed invention: "(1) the quantity of experimentation necessary, (2) the amount and direction of guidance provided, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988).

With respect to the relative skill in the art, it is clear that the relative skill in art of generating variant polypeptides is very high. For example, those skilled in the art are aware of various random mutagenesis protocols can be used to create libraries of clones encoding variant polypeptides.

With respect to the guidance provided by the specification, by providing a simple, high throughput screening method, the specification provides considerable guidance in the generation and screening of variant polypeptides.

With respect to the absence or presence of working examples, the specification provides a working example of successful high throughput screening for the identification of nucleic acids encoding toxic peptides.

Regarding the breadth of the claims, it is Applicants' position that the claims are not excessively broad encompassing as they do nucleic acid molecules encoding polypeptides having at least 70% (75%, 80%, 85%, 90%, 95%, or 98%) to a reference polypeptide (SEQ ID NO:22 or SEQ ID NO:23).

With respect to predictability, although it cannot always be predicted whether a given amino acid change will alter function, it is generally understood, despite some exceptions, that certain types of variants, e.g., those involving conservative amino acid substitutions are more likely to retain function.

With respect to the amount of experimentation required, the high through-put screening methods described in the present specification are capable of testing many, many peptides very rapidly. There are two reasons for this. First, the assay itself is quite simple in so much as it involves simply exposing nematodes to a clone expressing the polypeptide of interest. Second, as of the priority date of the present application, 1999, technology was available to rapidly generate large libraries of variant polypeptides.

The Examiner relies on Rudiger to support the assertion that practicing the present invention would require undue experimentation. Rudiger was published in 1976, almost three decades ago. In 1976 it may have required "painstaking experimental study" to identify active variants of any given protein. However, this was only shortly after Cohen and Boyer published their first papers describing gene cloning in 1973 and 1974. Thus, in 1976 it was undoubtedly difficult to produce, much less test, variant polypeptides. In the 23 years between the publication of Rudiger and the 1999 priority date of the present application, there was been a molecular biology revolution that made the generation of libraries of variant polypeptides routine. Today,

companies sell kits that allow one of ordinary skill in the art to readily generate libraries of variants of any selected gene. Rudiger's statements are simply no longer even remotely relevant.

Consideration of the *Wands* factors leads to the conclusion that the specification enables one of ordinary skill in the art to make and to use the invention.

In view of the forgoing, Applicants respectfully request that the enablement rejections under 35 U.S.C. §112, first paragraph be withdrawn.

Rejections Under 35 U.S.C. §112, second paragraph

The Examiner rejected previously pending claims 13, 14, and 29 under 35 U.S.C. §112, second paragraph as allegedly indefinite.

The Examiner stated that previously pending claims 13 and 14 are indefinite because they do not recite a reference sequence. Claims 13 and 14 have been cancelled. The currently pending claims recite a reference sequence.

The Examiner stated that previously pending claim 29 is indefinite because it does not include a step relating back to the preamble. New claim 53 is drawn to a method for producing a polypeptide. The last step of this claim properly refers to the production of a polypeptide and is believed to meet the requirements of 35 U.S.C. §112, second paragraph.

In view of the forgoing, Applicants respectfully request that the indefiniteness rejections under 35 U.S.C. §112, second paragraph be withdrawn.

Rejections Under 35 U.S.C. §102

The Examiner rejected previously pending claims 12-16 and 19 under 35 U.S.C. §102(e) allegedly anticipated by Geoghegan et al. (U.S. Patent 6,006,470); under 35 U.S.C. §102(b) allegedly anticipated by Narva et al. (U.S. Patent 5,236,843); and under 35 U.S.C. §102(b) allegedly anticipated by Jarrett et al. (WO 98/08388). The Examiner stated that Geoghegan et al. and Narva et al. disclose peptides toxic to nematodes, and that these disclosures anticipate the variants of claims 12-16 and 29. The Examiner stated that Jarrett et al. teaches an *Xenorhabdus* nucleic acid molecule encoding a toxin that has insecticidal properties and that this meets the

limitations of the previously pending claims since, according to the Examiner, the claims require 70% homology to an unknown protein.

Geoghegan et al. describe mannose-binding lectins derived from *Amarylliaceae*, *Alliaceae*, and *Vicieae* that are said to be toxic to nematodes. Narva et al. describe nematode toxins derived from *B. thuringiensis*. It does not appear that any of these peptides anticipate the presently pending claims.

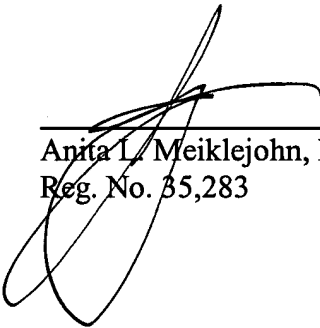
Jarrett et al. describes *X. nematophilus* peptides that are said to have insecticidal activity against certain insects. It does not appear that any of these peptides anticipate the presently pending claims.

In view of the forgoing, Applicants respectfully request that the rejections under 35 U.S.C. §102 be withdrawn.

Enclosed is a Petition for Extension of Time with the appropriate fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 10 Feb 04

  
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Anita L. Meiklejohn, Ph.D.  
Reg. No. 35,283

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Telephone: (617) 542-5070  
Facsimile: (617) 542-8906

# NCIMB LTD

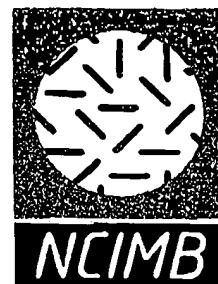
Our ref: PAT 163/NCPAT 10458

Your ref: Order N : 30377/PJ

Date: 9 November 1998

Dr Simon Kremer  
Mewburn Ellis Patent Agents  
No. 1 Redcliff Street  
Bristol  
BS1 6NP

Dear Sir/Madam



## NOTIFICATION OF ACCEPTANCE OF A DEPOSIT FOR THE PURPOSES OF PATENT PROCEDURE

Microorganism	Strain Number	NCIMB Number
<i>Xenorhabdus bovienii</i>	H31	NCIMB 40985
<i>Xenorhabdus bovienii</i>	I73	NCIMB 40986

I have to inform you that the above designated microorganism(s), received on 5 November 1998 was accepted for deposit for patent purposes on 5 November 1998. You are reminded that you are bound by the terms and conditions of this acceptance set out in the Application Form signed by \* on 4 November 1998 a copy of which should have been retained by you.

Yours faithfully

Gordon McFarlane.

\* Dr Paul Jarrett  
Horticulture Research International  
Wellesbourne  
Warwickshire  
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Aberdeen AB24 3RY  
Scotland, UK  
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E-mail [ncimb@abdn.ac.uk](mailto:ncimb@abdn.ac.uk)  
Internet address:  
<http://www.abdn.ac.uk/~aur014/ncimb.htm>

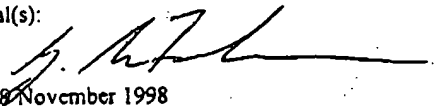
**BUDAPEST TREATY ON THE INTERNATIONAL  
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS  
FOR THE PURPOSES OF PATENT PROCEDURE**

Horticulture Research International  
Wellesbourne  
Warwickshire  
CV35 9EF

**INTERNATIONAL FORM**

**RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT**  
issued pursuant to Rule 7.1 by the  
**INTERNATIONAL DEPOSITARY AUTHORITY**  
identified at the bottom of this page

NAME AND ADDRESS  
OF DEPOSITOR

<b>I. IDENTIFICATION OF THE MICROORGANISM</b>	
Identification reference given by the DEPOSITOR:  <i>Xenorhabdus bovienii</i> H31	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:  NCIMB 40985
<b>II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION</b>	
The microorganism identified under I above was accompanied by:  <div style="display: flex; align-items: flex-start;"><div style="margin-right: 10px;"><input type="checkbox"/> <input checked="" type="checkbox"/></div><div> a scientific description  a proposed taxonomic designation</div></div> <p>(Mark with a cross where applicable)</p>	
<b>III. RECEIPT AND ACCEPTANCE</b>	
This International Depositary Authority accepts the microorganism identified under I above, which was received by it on 5 November 1998 (date of the original deposit) <sup>1</sup>	
<b>IV. RECEIPT OF REQUEST FOR CONVERSION</b>	
The microorganism identified under I above was received by this International Depositary Authority on (date of the original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion)	
<b>V. INTERNATIONAL DEPOSITARY AUTHORITY</b>	
Name: NCIMB Ltd.,  Address: 23 St Machar Drive, Aberdeen, AB24 3RY, Scotland.	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s):  Date: 8 November 1998

<sup>1</sup> Where Rule 6/4(d) applies, such date is the date on which the status of International Depositary Authority was acquired.


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**NAME AND ADDRESS  
OF DEPOSITOR**

<b>I. IDENTIFICATION OF THE MICROORGANISM</b>	
Identification reference given by the DEPOSITOR:  <i>Xenorhabdus bovienii</i> 173	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:  NCIMB 40986
<b>II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION</b>	
The microorganism identified under I above was accompanied by:  <input type="checkbox"/> a scientific description  <input checked="" type="checkbox"/> a proposed taxonomic designation  (Mark with a cross where applicable)	
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Name: NCIMB Ltd.,  Address: 23 St Machar Drive, Aberdeen, AB24 3RY, Scotland.	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s):  Date: 9 November 1998

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**INTERNATIONAL FORM**

**VIABILITY STATEMENT**

issued pursuant to Rule 10.2 by the  
**INTERNATIONAL DEPOSITARY AUTHORITY**  
identified on the following page

NAME AND ADDRESS OF THE PARTY  
TO WHOM THE VIABILITY STATEMENT  
IS ISSUED

<b>I. DEPOSITOR</b>	<b>II. IDENTIFICATION OF THE MICROORGANISM</b>
Name: AS ABOVE Address:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: NCIMB 40985  Date of the deposit or of the transfer <sup>1</sup> :  5 November 1998
<b>III. VIABILITY STATEMENT</b>	
<p>The viability of the microorganism identified under II above was tested on 6 November 1998 <sup>2</sup>. On that date, the said microorganism was:</p> <p><sup>3</sup></p> <p><input checked="" type="checkbox"/> viable</p> <p><sup>3</sup></p> <p><input type="checkbox"/> no longer viable</p>	

- <sup>1</sup> Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).
- <sup>2</sup> In the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability test.
- <sup>3</sup> Mark with a cross the applicable box.

IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED<sup>4</sup>

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: NCIMB Ltd.,

Address: 23 St Machar Drive,  
Aberdeen.  
A24 3RY,  
Scotland.

Signature(s) of person(s) having the power  
to represent the International Depositary  
Authority or of authorised official(s):

  
Date: 9 November 1998

<sup>4</sup> Fill in if the information has been requested and if the results of the test were negative.

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CV35 9EF

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Name: AS ABOVE Address:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: NCIMB 40986  Date of the deposit or of the transfer <sup>1</sup> : 5 November 1998
<b>III. VIABILITY STATEMENT</b>	
<p>The viability of the microorganism identified under II above was tested on 6 November 1998<sup>2</sup>. On that date, the said microorganism was:</p> <p>3</p> <p><input checked="" type="checkbox"/> viable</p> <p>3</p> <p><input type="checkbox"/> no longer viable</p>	

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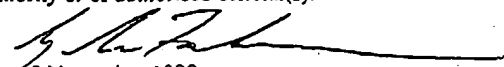
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to represent the International Depositary  
Authority or of authorised official(s):

  
Date: 9 November 1998

4 Fill in if the information has been requested and if the results of the test were negative.

# NCIMB LTD

Our ref: PAT 163/NCPAT 10824

Your ref: Order No: JAWM/32251/MB

Date: 22 January 1999

Dr Simon Kremer  
Mewburn Ellis Patent Agents  
No. 1 Redcliff Street  
Bristol  
BS1 6NP

Dear Sir/Madam



## NOTIFICATION OF ACCEPTANCE OF A DEPOSIT FOR THE PURPOSES OF PATENT PROCEDURE

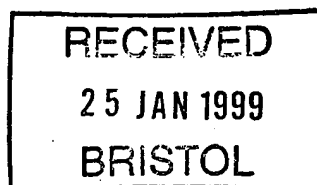
Microorganism	Strain Number	NCIMB Number
<i>Xenorhabdus</i> species	C42	NCIMB 41004

I have to inform you that the above designated microorganism(s), received on 20 January 1999 was accepted for deposit for patent purposes on 20 January 1999. You are reminded that you are bound by the terms and conditions of this acceptance set out in the Application Form signed by \* on 20 January 1999 a copy of which should have been retained by you.

Yours faithfully

Gordon McFarlane.

\* Dr J A W Morgan  
Plant Pathology and Microbiology  
Horticulture Research International  
Wellesbourne  
Warwickshire  
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E-mail [ncimb@abdn.ac.uk](mailto:ncimb@abdn.ac.uk)  
Internet address:  
<http://www.abdn.ac.uk/~aur014/ncimb.htm>


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NAME AND ADDRESS  
OF DEPOSITOR

<b>I. IDENTIFICATION OF THE MICROORGANISM</b>	
Identification reference given by the DEPOSITOR:  <i>Xenorhabdus</i> species C42	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:  NCIMB 41004
<b>II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION</b>	
The microorganism identified under I above was accompanied by:  <input type="checkbox"/> a scientific description  <input checked="" type="checkbox"/> a proposed taxonomic designation  (Mark with a cross where applicable)	
<b>III. RECEIPT AND ACCEPTANCE</b>	
This International Depositary Authority accepts the microorganism identified under I above, which was received by it on 20 January 1999 (date of the original deposit) <sup>1</sup>	
<b>IV. RECEIPT OF REQUEST FOR CONVERSION</b>	
The microorganism identified under I above was received by this International Depositary Authority on (date of the original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion)	
<b>V. INTERNATIONAL DEPOSITARY AUTHORITY</b>	
Name: NCIMB Ltd.,  Address: 23 St Machar Drive, Aberdeen, AB24 3RY, Scotland.	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s):  Date: 22 January 1999

<sup>1</sup> Where Rule 6/4(d) applies, such date is the date on which the status of International Depositary Authority was acquired.

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<b>I. DEPOSITOR</b>	<b>II. IDENTIFICATION OF THE MICROORGANISM</b>
Name: AS ABOVE Address:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: NCIMB 41004  Date of the deposit or of the transfer <sup>1</sup> : 20 January 1999
<b>III. VIABILITY STATEMENT</b>	
<p>The viability of the microorganism identified under II above was tested on 21 January 1999 <sup>2</sup>. On that date, the said microorganism was:</p> <p>3</p> <p><input checked="" type="checkbox"/> viable</p> <p>3</p> <p><input type="checkbox"/> no longer viable</p>	

- 1 Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).
- 2 In the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability test.
- 3 Mark with a cross the applicable box.


IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED<sup>4</sup>

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Address: 23 St Machar Drive,  
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A24 3RY,  
Scotland.

Signature(s) of person(s) having the power  
to represent the International Depositary  
Authority or of authorised official(s):

  
Date: 22 January 1999

4. Fill in if the information has been requested and if the results of the test were negative.